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CLINICAL REVIEW

Sleep disordered breathing in Parkinson's disease: A critical appraisal

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SUMMARY

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by resting tremor, rigidity, bradykinesia and postural instability, and is associated with non-motor features, including sleep abnormalities. The high prevalence of excessive daytime sleepiness and snoring in PD patients has led to the suggestion that sleep disordered breathing (SDB) is more common in these individuals than in normal subjects. We aimed to review the literature on SDB prevalence and its clinical repercussions in PD. A PubMed search was performed to identify controlled studies, published from January 1990 through October 2012, which addressed the prevalence of SDB diagnosed by polysomnography in idiopathic PD. From the seven studies included, five reported similar or lower prevalence of SDB in patients when compared to healthy age-matched controls. Two studies reported less oxyhemoglobin desaturation during sleep among patients. These results did not support the idea that PD patients are at increased risk of SDB and indicate that they may not present significant hypoxemia. The prevalence of obstructive sleep apnea syndrome and the long-term outcomes of disordered breathing events during sleep have not been adequately studied in PD.

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder, affects about 1–2% of adults over 60.[1,2]Although the diagnosis still depends on the detection of motor features of resting tremor, cogwheel rigidity, bradykinesia and postural instability, non-motor manifestations are highly prevalent and often cause significant disability.[3–6] These include autonomic and neuropsychiatric symptoms, pain, fatigue and sleep abnormalities.[7]

Sleep problems are very frequent complaints of PD patients, the most common being sleep fragmentation.[8–10] REM sleep behavior disorder (RBD) and excessive daytime sleepiness (EDS) are also widely recognized as more prevalent in PD patients than controls and may even predate the onset of the motor symptoms.[11–13]

Nevertheless, the clinical significance of sleep disordered breathing (SDB) in PD remains an issue of debate. Considering that snoring was reported by up to 70% of PD patients, it would be reasonable to hypothesize that they have an increased risk of developing obstructive sleep apnea (OSA),[14,15] but studies have yielded conflicting results.[16–18] As disordered breathing events in sleep are highly prevalent in the general population, mainly among people over 60,[19] a high prevalence of SDB in PD may reflect the underlying aging process rather than the PD pathology.

A number of reasons underscore the importance of studying the interactions between OSA and PD. There is increasing evidence that OSA may negatively impact on cardiovascular health.[20,21] OSA causes cognitive dysfunction, which is another common non-motor feature of PD and significantly decreases quality of life.[22] Moreover, OSA consequences may extend beyond general health into motor performance of PD patients. Oxidative stress and inflammation, two mechanisms linking OSA and cardiovascular diseases, are also known to be involved in PD pathophysiology.[23,24] Experimental data reinforces the role of oxidative stress on alfa-synuclein aggregation and dopaminergic cell death.[25]

Our primary objective was to review studies on the prevalence of SDB in PD. Specifically, we aimed to investigate whether SDB is more prevalent in PD than in the general population. As a secondary outcome, whenever reported, we assessed if there was any difference in clinical repercussions of SDB between PD patients and healthy individuals.

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List of abbreviations

BMI	body mass index
EDS	excessive daytime sleepiness
HY	Hoehn and Yahr
OSA	obstructive sleep apnea
OxyHb	oxyhemoglobin
PD	Parkinson's disease
PSG	polysomnography
RBD	REM sleep behavior disorder
RDI	respiratory disturbance index
REM	rapid eye movement
SDB	sleep disordered breathing
UPDRS	unified Parkinson's disease rating scale

Methods

A PubMed literature search of publications between January 1990 through October 2012 was performed to identify controlled cross-sectional and longitudinal studies addressing the prevalence of SDB in idiopathic PD as the primary outcome or one of the outcome measures. We used the terms "sleep disordered breathing", "obstructive sleep apnea", "sleep apnea" and "Parkinson disease". Abstracts were reviewed to assess eligibility and reference lists were screened to find additional relevant articles. Only studies using polysomnography (PSG) were included. Papers written in languages other than English, case reports and review articles were excluded.

Results

Search results

Our search strategy identified 110 publications. Fourteen articles were screened for eligibility (Fig. 1), seven of which were included, with a cumulative total of 347 patients (Table 1).[15,26–31] Mean disease duration ranged from 6 to 8.3 years. Different measures of PD severity were used: Hoehn and Yahr (HY) score (mean from 2.00 ± 0.7 through 2.6 ± 0.8 or median 2.5)[26–28,31] and the unified Parkinson's disease rating scale (UPDRS) score (mean from 16.8 ± 10.1 through 27.6 ± 16 or categories <12: 53%; 12–22: 40% and >22: 7%).[15,29,31] In one study, authors did not report the severity of the disease in their patients.[30] All patients were on antiparkinsonian therapy, except the 26 from the study by Ferini-Strambi et al.[26]

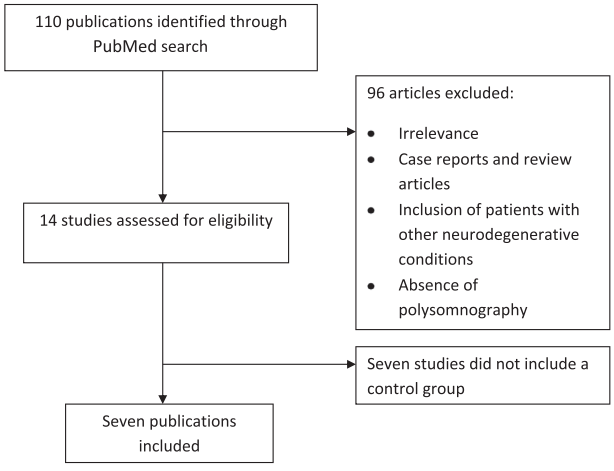

Fig. 1. Flow chart representing the process of selection of studies for inclusion in the review.

Five cross-sectional studies[32–36] and two trials[37,38] were excluded on the basis of absence of a control group of healthy subjects. (Table 2)

No longitudinal study on SDB in PD was identified.

Methodological issues

Patients and controls were matched with regard to age and gender. Body mass index (BMI) was similarly matched between the groups, except for the study by Diederich et al., in which patients and controls were matched for apnea–hypopnea index (AHI),[27] and the study by Shpirer et al.,[28] in which BMI for patients and controls were not specified. In the study by Diederich et al., controls had a greater BMI than patients (28.5 ± 6.72 vs 25.75 ± 4.34 kg/m^2, $p = 0.04$). In one paper,[30] patients were compared to previously published normative data.[39]

In one study, pulmonary function tests were performed one hour after levodopa administration.[15] Patients did not differ with regard to spirometric results when compared to controls, but presented lower maximum inspiratory and expiratory mouth pressures, indicating respiratory muscle weakness.

In two studies, the PSG criteria for respiratory events were not established.[26,31] Definition of hypopnea varied among the remainder (Table 1). Those for apnea were more similar among studies, including complete or almost complete cessation of airflow lasting 10 s or more,[15,28–30] associated with oxyhemoglobin (oxyHb) desaturation of at least four percent.[27]

A reliable blinding method to assess PSG data from patients and controls was reported only in the study by Shpirer et al.[28]

SDB prevalence

The SDB rates among PD patients are shown in Table 1. Five studies showed that PD patients have a similar or even smaller amount of obstructive apneas and hypopneas during sleep than controls.[26,27,29–31]

The study by Maria et al.[15] reported a greater median AHI for PD patients (11 vs 5.7 events/h, $p = 0.048$). Nine out of 15 patients (60%) presented moderate SDB (15 < AHI < 30 events/h), none had severe SDB (AHI > 30 events/h) and one (6%) had central sleep apnea. Shpirer et al.[28] found a greater AHI for patients when compared to controls (7.9 ± 12.5 vs 2.7 ± 3.2 events/h, $p = 0.01$), but authors did not state if patients and controls were matched for BMI. It is noteworthy that even in the PD group a low mean AHI level was found.

Four studies investigated central sleep apnea and none of them found a higher index for PD patients.[15,27,29,31]

In the study by De Cock et al.,[29] patients with increased chin muscle tone during REM sleep tended to have higher AHI than those with normal muscle atonia (18.2 ± 15.9 vs 6.8 ± 10.7 events/h, $p = 0.05$). OSA was found even during REM sleep. No study reported AHI for REM and non-REM sleep stages separately.

Relationship with motor dysfunction parameters and clinical repercussions of SDB

A significant correlation between the severity of PD and AHI was reported by Maria et al.[15] However, their study included a small sample size (15 patients) and five out of 10 patients with SDB had mild PD. De Cock et al.[29] also reported that patients with greater motor disability were more likely to have SDB. Conversely,

Table 1
Characteristics and results of seven controlled cross-sectional studies on sleep disordered breathing among Parkinson's disease patients.

Authors (country)	Patients *n* (mean age) (M/F)	Normal controls *n* (mean age) (M/F)	Mean BMI (patients vs controls, kg/m^2)	Hypopnea definition[a]	Results
Ferini-Strambi et al., 1992 (Italy)[26]	26 (64.7y) 11/15	15 (63.1y) 7/8	27.1 vs 27.4	Not stated	RDI > 10 events/h in 30.7% of patients. Similar mean RDI between groups; no difference in oxyHb saturation.
Maria et al., 2003 (Greece)[15]	15 (63y) 12/3	15 (60y) 12/3	27 vs 27	>50% Airflow decrease + ≥4% desaturation, ≥10 s	Ten patients (66%) with AHI > 5 events/h. In 9 (60%), AHI between 15 and 30 events/h. Greater median AHI in PD ($p = 0.048$); median sleep oxyHb saturation 93%.
Diederich et al., 2005 (Luxembourg)[27]	49 (64.9y) 38/11	49 (61.3y) 38/11	25.7 vs 28.5	>20% flow decrease + ≥4% desaturation, ≥10s	AHI > 5 events/h was found in 21 patients (43%). Patients had less frequent SDB; they also maintained higher mean oxyHb saturation (except when BMI > 27 kg/m^2).
Shpirer et al., 2006 (Israel)[28]	46 (67.3y) 23/23	30 (65.2y) 18/12	Not stated	>50% airflow decrease + (≥3% desaturation or arousal), ≥10 s	Mean AHI was greater for PD patients (7.9 vs 2.7 events/h, $p = 0.01$). AHI > 10 events/h in 21.7% of patients.
De Cock et al., 2010 (France)[29]	100 (62y)[b] 70/30	50 (62y) 35/15	24.5 (unselected) vs 24.8 (sleepy) vs 24.7 (controls)	>50% airflow decrease + (≥3% desaturation or arousal), ≥10 s	Patients had less SDB than controls (27% vs 40%), lower AHI and higher nadir oxyHb saturation.
Trotti and Bliwise, 2010 (USA)[30]	55 (63.9y) 37/18	Normative data[c]	26.8 vs 28.5	≥30% flow decrease + ≥4% desaturation, ≥ 10 s	AHI > 5 events/h in 43.6% of patients (14.5% with AHI ≥ 15 events/h). PD patients did not have more SDB than controls.
Yong et al., 2011 (Singapore)[31]	56 (65.4y) 34/22	68 (59.3y) 38/20	22.8 vs 23.9	Not stated	No difference in AHI between groups; prevalences of SDB were 49.1 and 65.7% for patients and controls, respectively.

AHI, apnea-hypopnea index; BMI, body mass index; M/F, male to female; *n*, number of patients; oxyHb, oxyhemoglobin; PD, Parkinson's disease; RDI, respiratory disturbance index; SDB, sleep disordered breathing.
[a] Different hypopnea criteria were used. Apnea definitions were more uniform.
[b] Fifty PD patients were unselected and 50 were referred for sleepiness.
[c] Adults from the Sleep Heart Health Study ($n = 6132$; mean age 62.9y; 47.2% male).

patients with AHI > 15 events/h had a shorter disease duration in another study.[30] No association between PSG parameters and PD severity was found by Yong et al.[31] Three studies did not address this subject.[26–28]

Three investigations have not reported oxyHb saturation measurements during sleep.[28,30,31] In one study, median and nadir oxyHb saturation were lower for patients (93% *vs* 96%, $p = 0.0003$ and 90 vs 92%, $p = 0.002$, respectively).[15] The other three studies

Table 2
Characteristics and results of seven cross-sectional studies on sleep disordered breathing among Parkinson's disease patients. These studies did not include a control group of normal individuals for comparison.

Authors (country)	Patients n (mean age) (M/F)	Mean BMI (kg/m^2)	Hypopnea definition[a]	Results
Arnulf et al., 2002 (France)[33]	54 (68y)[b] 44/10	25	>50% airflow decrease or <50% + (≥ 4% desaturation or arousal)	AHI > 15 events/h in 20% of patients.
Young et al., 2002 (Australia)[32]	18 (69.2 and 70y)[c] 10/8	Not stated	<80% airflow decrease + ≥2% desaturation, ≥10 s	Mean AHI were 2.7 and 2.6 events/h for patients with mild and severe PD, respectively.
Medeiros et al., 2007 (Brazil)[38]	18 (61.8y) 16/2	Not stated	Not stated	About 45% of patients presented AHI > 15 events/h, but no severe oxyhemoglobin desaturation was found.
Ondo et al., 2008 (USA)[37]	38 (not stated)[d] not stated	Not stated	>30% airflow reduction + (≥3% desaturation or arousal), ≥10 s	AHI > 15 events/h was found in 7/38 (18.4%) patients.
Norlinah et al., 2009 (Malaysia)[34]	46 (64y) 27/19	24.4	>50% nasal airflow decrease, ≥10 s	SDB was diagnosed in 24 (52%) patients. Twelve patients (26%) had AHI > 15 events/h.
Poryazova et al., 2010 (Switzerland)[35]	30 (65y) 24/6	Not stated	>50% airflow decrease or <50% + (≥4% desaturation or arousal)	AHI > 10 events/h was found in 10 (33%) patients.
Lelieveld et al., 2012 (USA)[36]	51 (63.9y) 43/8	28	≥30% airflow reduction + ≥4% desaturation or ≥50% airflow reduction + (≥3% desaturation or arousal), >10 s	Mean RDI (including apnea, hypopnea and RERA) was 23 events/h. RDI > 15 events/h was found in 33 (64.7%) patients.

AHI, apnea-hypopnea index; BMI, body mass index; M/F, male to female; *n*, number of patients; PD, Parkinson's disease; RDI, respiratory disturbance index; RERA, respiratory event-related arousal; SDB, sleep disordered breathing.
[a] Different hypopnea criteria were used. Apnea definitions were more uniform.
[b] All patients were referred for sleepiness.
[c] Mean ages for patients with mild and severe PD, respectively.
[d] Eight patients were excluded from the trial (seven presented AHI > 15). Thirty patients completed the study (mean age 61.5y, 24 men).

showed no difference between patients and controls in nadir oxyHb saturation and time spent with saturation <95%[26] or higher mean and nadir oxyHb saturation among patients.[27,29] In the study by Diederich et al.,[27] reduced oxyHb saturation was only observed in PD patients with BMI > 27 kg/m^2.

Symptoms that characterize the presence of OSA syndrome were investigated in two studies. In one study, all patients with AHI > 5 events/h (10 out of 15; 9 with obstructive events) presented daytime sleepiness, choking or gasping during sleep, daytime fatigue, unrefreshing sleep or recurrent awakenings from sleep.[15] In the other, snoring and unrefreshing sleep were observed respectively in 96.2 and 38.4% of PD patients with AHI > 5 events/h.[31]

Only one investigation addressed chronic repercussions of SDB in PD patients. When comparing those with and without SDB, no significant difference was found with regard to cardiovascular diseases, including arterial hypertension, coronary heart disease and stroke. Nevertheless, these conditions tended to be more prevalent among patients with SDB ($p = 0.07$).[29]

SDB prevalence (excluded studies)

In one study, all PD patients had normal AHI.[32] The prevalence of moderate to severe SDB (AHI > 15 events/h) ranged from 20 to 45%.[33,34,37,38] Ten out of 30 patients (33%) presented AHI > 10 events/h in another investigation.[35] Mean respiratory disturbance index (RDI) was 23 events/h among 51 PD patients in the study by Lelieveld et al.,[36] with rates of mild (5 < RDI < 15 events/h), moderate (15 < RDI < 30 events/h) and severe (RDI > 30 events/h) SDB of 11.7, 39.2 and 25.5%, respectively. The lack of a control group and differences in patient characteristics and methods hamper analysis of these results. For instance, hypopnea definition has been shown to have a significant impact on AHI.[40]

Discussion

Damage to neurons of substantia nigra, which is the hallmark of PD, is accompanied by extensive loss of neurons in extranigral sites, including brainstem nuclei involved in sleep physiology and respiratory control.[16,41] Respiratory dysfunction, including restrictive and obstructive abnormalities and upper airway obstruction, which are improved by apomorphine and levodopa, has long been demonstrated in PD.[42–45] These observations, together with the high proportion of patients presenting EDS and snoring,[14,33]confers biological and clinical plausibility to the assumption that PD patients are at a greater risk of SDB. Nevertheless, the findings of the present review do not support this hypothesis.

Indeed, neither obstructive nor central disordered breathing events were more frequent in PD patients than age-matched controls. Only two investigations have looked for symptoms that indicate the presence of OSA syndrome and the rates were not compared with those among control subjects. However, studies have not shown significant oxyHb desaturation, except when obesity is present.[27] Some protective factors have been pointed out in the literature that may explain these results.

Firstly, PD patients usually have lower BMI than controls, as it has been shown in a recent meta-analysis.[46] In addition to this, muscle atonia during REM sleep, which facilitates upper airway collapse, is a mechanism underpinning the disordered breathing events occurring in this stage of sleep.[47,48] Disordered breathing events during REM sleep have been shown to be prolonged and induce severe oxyHb desaturation by some authors,[49,50] but not by others.[51,52] Loss of muscle atonia during REM sleep in some PD patients could render them less vulnerable to apneas and hypopneas, as it has been shown for patients with RBD and OSA without PD.[53] Nonetheless, PD patients with increased muscle tone during REM sleep still present obstructive apneas.[29] Finally, it has been said that deficient respiratory coordination during sleep, secondary to parkinsonian motor symptoms or medications, could be misdiagnosed as apneic events, explaining the lack of significant oxyHb desaturation during sleep.[27] In the absence of confirming studies, this hypothesis remains speculative.

It could be argued that studies have usually included PD patients with mild or moderate disease and that more frequent SDB could be found in patients with severe motor symptoms. However, lack of association between AHI and PD duration and severity has been shown in two studies.[30,31] In a study specifically addressing differences in sleep problems between these two groups of patients, those with severe PD did not have greater AHI than those with mild PD.[32] Thus, SDB in PD does not seem to be a disease-related process, as is the case for RBD and EDS.[12,16] It is much more an aging-related condition.

It is well established that SDB is highly prevalent among elderly subjects, but studies on the morbidity and mortality in this age group are controversial, with some investigations indicating SDB is a serious problem, while others suggest a less negative impact on general health.[54–56] Moderate sleep apnea (RDI between 20 and 40 events/h) was even found to be associated with decreased mortality rate in elderly people.[57]The authors speculated that chronic hypoxia from apneic events may activate cardioprotective adaptative pathways, similar to the protection from infarction, arrhythmia and additional ischaemia conferred by repeated sublethal ischaemic insults.

Besides the tendency for lower BMI referred to above, other distinctive characteristics of PD patients may lead to different long-term outcomes when compared to elderly controls. For instance, cardiac sympathetic denervation is an early non-motor feature of PD.[58] Sympathetic influence on heart rate variability is reduced during REM and non-REM sleep in PD patients.[59] As increased sympathetic activity from recurrent apnea and hypopnea-associated hypoxemia plays an important role in increased cardiovascular risk,[20,60] it has been claimed that cardiac denervation may protect PD patients with sleep apnea from cardiovascular diseases.[61] However, in one study, a tendency for a greater prevalence of cardiovascular events (hypertension, coronary heart disease and stroke) among PD patients with SDB, when compared to patients without SDB, was found.[29] The long-term impact of SDB on PD patients, including cardiometabolic and cognitive outcomes, has not yet been properly addressed. Also, it would be valuable to know if SDB impacts on the evolution of PD motor features.

EDS does not correlate with AHI in PD. It may be considered an integral part of PD and should not be assigned as indicative of SDB in PD patients.[12]In this case, continuous positive airway pressure devices may be of no value in some PD patients with hypersomnolence. These findings, along with the lack of information on SDB consequences for PD patients, have important implications for the assessment and treatment of those with these two conditions. Patients with unequivocal evidence of symptomatic SDB must receive treatment, whereas those with uncertain symptoms should be investigated further.[62]

In summary, evidence indicates that individuals with PD are not at a greater risk of developing disordered breathing events during sleep and that less pronounced acute effects may arise from these events when compared to other elderly adults. There is a paucity of data regarding the prevalence of OSA syndrome and the long-term impact of SDB on the cardiovascular morbidity and mortality, cognitive function, motor symptoms and quality of life in PD. This is an area that warrants further investigation.

Practice points

- Prevalence of sleep disordered breathing is not greater in Parkinson's disease patients when compared to age and gender-matched controls.
- Some studies have shown that disordered breathing events in sleep are associated with less significant oxyhemoglobin desaturation among Parkinson's disease patients.

Research agenda

- Studies looking in to the rate of obstructive sleep apnea syndrome and the impact of sleep disordered breathing on the cardiovascular morbidity and mortality, cognitive function, motor symptoms and quality of life in Parkinson's disease are warranted.

Conflicts of interest

The authors declare no conflict of interest.

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